

MODEL APPLICATIONS TO MANUFACTURE PET DRUGS FOR MARKETING

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PET DRUG PRODUCTS FOR MODEL APPLICATIONS

- **Fludeoxyglucose F 18 Injection**
- **Ammonia N 13 Injection**
- **Sodium Fluoride F 18 Injection**

TYPES OF APPLICATIONS

- **New Drug Application (NDA) - 505(b)(2)**
- **Abbreviated New Drug Application (ANDA) - 505(j)**
- **Guidance - Which, What, How & Where**
- **Model Chemistry, Manufacturing , and Controls (CMC) Section - Used for NDA or ANDA**

MODEL APPLICATIONS FOR PET DRUGS - CMC SECTION

- Is Submitted With Cover Letter, Forms, Certifications, and Other Information - Details in Guidance**
- Provide Guidance for Content and Format of Chemistry, Manufacturing, and Controls (CMC) for Indicated PET Drugs**

CMC - LIST OF SUBSECTIONS

1. Drug Product Components and Quantitative Composition
2. Controls for Components / Raw Material
3. Reference Standards
4. Manufacturing and Testing Facilities
5. Manufacture of Drug Substance
6. Manufacture of Drug Product
7. Container / Closure
8. Controls for Finished Dosage Form
9. Description of Analytical Test Procedures
10. Microbiological Validation
11. Stability and Batch Data
12. Vial and Outer Packaging Labels
13. Environmental Assessment

1. DRUG PRODUCT COMPONENTS AND QUANTITATIVE COMPOSITION

- Drug Substance
- Other Ingredients
- Composition/mL (Range of mCi/mL @ EOS)
- Composition / Batch (Range of mCi @ EOS & Volume)
 - ^{18}F -FDG, Na^{18}F
- Composition/batch Subportion Vial (Range of mCi @ EOS & Volume) - $^{13}\text{NH}_3$

2. CONTROLS FOR COMPONENTS / RAW MATERIALS

- **^{18}F -FDG**
 - **Organic Substrate (e.g., Mannose Triflate)**
 - **Target Material (e.g., H_2^{18}O)**
 - **Radioactive Fluoride Reagent**
 - **Other Ingredients**
 - **Reagents, Solvents, Gases, Purification Columns, and Other Auxiliary Materials**

2. CONTROLS FOR COMPONENTS / RAW MATERIALS

- **$^{13}\text{NH}_3$ and Na^{18}F**
 - **Target Material**
 - **Other Ingredients**
 - **Reagents, Solvents, Gases, Purification Columns, and Other Auxiliary Materials**
- **Na^{18}F - If Obtained From Outside Source**
 - **Complete Information Will Need to Be Provided**

3. REFERENCE STANDARDS

- **Used to Establish**
 - **Identity of a Component**
 - **Assay (Amount) of a Component**
- **Name & Address of Supplier**
- **Certificate of Analysis**
- **Acceptance Criteria**

4. MANUFACTURING AND TESTING FACILITIES

- **Name and Address of PET Drug Product Production and Testing Facilities**
- **Name of Contact Person**
- **Phone Number of Contact Person**

5. MANUFACTURE OF DRUG SUBSTANCE

A. Batch Formula

- **Name of Each Component**
- **Component's Function**
- **Amount Used**

B. Production of Radionuclide

- **Make and Model of Cyclotron**
- **Operating Parameters**
- **Specifications for Target Body**

5. MANUFACTURE OF DRUG SUBSTANCE

C. Synthesis & Purification of Drug Substance

- Radiochemical Synthesis & Purification Equipment**
 - Description**
 - Flow Diagram**
 - Acceptance Criteria for Components**
- Radiochemical Synthesis & Purification Operation**
- In-process Controls**
- Post Synthesis Procedures**

6. MANUFACTURE OF DRUG PRODUCT

- **Production Operation**
 - **Formulation Process**
 - **Copy of Master Production and Control Records**
- **Reprocessing of PET Drug Product**
- **Packaging and Labeling**

7. CONTAINER / CLOSURE

- **USP Type I Glass, Gray Butyl Rubber Stopper, Sterile, Pyrogen Free**
 - **Catalog Number**
 - **Name and Address of Supplier**
 - **DMF Number**
 - **Letter of Authorization**
 - **Acceptance Criteria**
- **Otherwise Full Information With Sterilization Procedures and Sterility Assurance**

8. CONTROLS FOR FINISHED DRUG PRODUCT

- **Sampling Procedures for Testing**
 - **^{18}F -FDG and Na^{18}F - How Much Volume and How Is It Distributed for Tests**
 - **$^{13}\text{NH}_3$**
 - **Each Batch May Be Produced in Multiple Subportions**
 - **Test First Subportion Provided Equivalency of All Subportions Is Validated, or**
 - **Test First and the Last Subportion for Each Batch**

8. CONTROLS FOR FINISHED DRUG PRODUCT

- **Regulatory Specifications, Procedures, and Testing Schedules**
 - **PET Drug Product Must Meet Acceptance Criteria Throughout Its Shelf Life When Tested According to the Procedures Described in the Application**
 - **Model Applications Provide Guidance for Acceptable Specifications**

8. CONTROLS FOR FINISHED DRUG PRODUCT

- Appearance
- Radionuclidic Identity
- Radiochemical Identity
- Radionuclidic Purity
- Radiochemical Purity
- Radiochemical Impurities
- Assay (Radioconcentration)
- Specific Activity
- pH
- Chemical Impurities
 - Residual Solvents
 - Process or Drug Related Impurities
 - Stereochemical Impurities
- Sterility
 - Sterility Testing
 - Membrane Filter Integrity
- Bacterial Endotoxins
- Tonicity

9. ANALYTICAL TEST PROCEDURES

- **Validated Standard Test Procedures (STPs)**
 - Analytical Supplies and Their Quality Used
 - All Equipment and Settings Used
 - Preparation of Test, Standard and Analytical Solutions
 - System Suitability Test- Schedule, Acceptance Criteria
 - Description of Test Procedures
 - Calculations (Formulae) in Quantitative Procedures
 - How the Results Are Reported
 - Validation Data

11. STABILITY & BATCH DATA

- **Expiration Dating Period Under Proposed Storage Conditions**
- **Stability/Batch Data**
 - **505(b)(2) Application - Release and Stability Data for three Batches at Upper Limit of the Proposed Radioconcentration Performed Under Proposed Storage Conditions**
 - **505(j) Application - Release Data for Three Batches and Stability for One of Them at Upper Limit of the Proposed Radioconcentration Performed Under Proposed Storage Conditions**

11. STABILITY & BATCH DATA

- **Post - Approval Commitments**
 - **A Minimum of One Batch/Year Tested for Stability According to Postapproval Stability Protocol**
 - **If a Batch Fails to Meet Acceptance Criteria Will Not Be Released and If Already Distributed Will Be Recalled From the Market**
 - **Any Changes to the Approved Application**
 - **21CFR314.70 (NDA)**
 - **21CFR314.97(ANDA)**

12. VIAL AND OUTER PACKAGING LABELS

- **Provide Draft Copies of**
 - **Draft Vial Labels**
 - **Draft Outer Packaging Labels**

12. VIAL AND OUTER PACKAGING LABEL'S CONTENT

- **Proprietary Name of the Drug Product - If Any**
- **Established Name of the Drug With Dosage Form**
- **Name and Address of the Manufacturer**
- **Strength (mCi/mL) at Calibration Time (EOS) and Total Radioactivity Amount**
- **Expiration Date / Time and Lot Number**
- **Statement - “Caution: Federal Law Prohibits Dispensing Without Prescription” or “Rx Only”**
- **Quantitative Composition**
- **Statement “For Intravenous Use”**
- **Radioactivity Warning Symbol**

13. ENVIRONMENTAL ASSESSMENT

- **Claim for Categorical Exclusion From Performance of EA Is Provided in the Model Application**